jnm/ PRELIMINARY NOTE

RADIATION DOSIMETRY OF ^{131}I-19-IODOCHOLESTEROL

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The only currently available radiopharmaceutical capable of locating the adrenal gland, imaging it, and quantitating its function is ^{131}I-19-iodocholesterol. To evaluate the relative radiation risk versus benefit, the absorbed radiation dose was calculated from pharmacokinetic human and animal data.

In an effort to develop an adrenal localizing agent, Counsell, et al (*1,2*) investigated the feasibility of radioiodinated steroids. The synthetic approach was to radiolabel naturally occurring compounds known to be biosynthesized and/or stored in the adrenals. In contrast to previously synthesized radioiodinated steroids, ^{125}I-19-iodocholesterol was found to resist in vivo deiodination while localizing in the adrenals.

The diagnostic use of ^{131}I-19-iodocholesterol has been extensively studied by Beierwaltes and coworkers. The tissue distribution in dogs has been completed (*3*). Iodine-131-19-iodocholesterol has been used to visualize human adrenal glands (*4,5*). The percentage uptake of radioactivity in the adrenal gland after administration of ^{131}I-19-iodocholesterol was determined by Morita, et al (*6*) using an Anger camera and a PDP 8/L computer. The position of aldosterone-producing tumors has been determined using ^{131}I-19-iodocholesterol (*7,8*). Adrenal remnants, the cause of persistent or recurrent Cushing's syndrome after "total" adrenalectomy, have been localized using ^{131}I-19-iodocholesterol (*9*).

Since use of ^{131}I-19-iodocholesterol is the only current method for imaging adrenals in patients allergic to contrast media and in identifying adrenal remnants, its benefit versus risk is maximized. In children or women of child bearing age due consideration should be given to the gonadal dose. In all other cases of adrenal scanning or adrenal function tests, the benefit versus risk should be considered against the hazards of adrenal venography. Adrenal venography requires hospitalization, induces pain, and in 5% of patients produces intra-adrenal hemorrhage with occasionally infarction of the adrenal.

METABOLISM

Tissue-distribution studies in dogs indicate increased concentrations of radioactivity in the thyroid gland suggestive of in vivo deiodination of ^{125}I-19-iodocholesterol. Extraction of adrenal cortices revealed no inorganic ^{125}I in the adrenals after injection of ^{125}I-19-iodocholesterol. Urine samples obtained from dogs treated with ^{125}I-19-iodocholesterol revealed no radioiodinated steroid metabolites, and all of the urinary radioactivity was accounted for as inorganic iodide (*2*).

Composite Day 1 urine samples from humans indicate predominate inorganic iodide ion. Composite daily urine samples Day 2 through Day 5 indicate several components similar to degradation products observed in accelerated decomposition studies (*10*).

RADIOCHEMICAL PURITY

Hotte and Ice (*10*) report a G-value of 2.6 and a heat of activation of 34.6 kilocalories/mole. The product has a projected 17-day shelf-life assuming a lower level of 70% as acceptable radiochemical purity.

NUCLEAR DATA FOR ^{131}I

Iodine-131 has a physical half-life of 8.05 days and emits five betas and nine gammas of varying energies. The radiation parameters used throughout the calculations were those presented in MIRD Pamphlet No. 4 considering only those gammas with an equilibrium dose constant greater than or equal

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TABLE 1. PARAMETERS ASSOCIATED WITH ^{131}I RADIATION (Ref. 11)

Radiation	n	Ē	Δ
beta 1	0.016	0.0701	0.0024
beta 2	0.069	0.0955	0.0140
beta 3	0.005	0.1428	0.0015
beta 4	0.904	0.1917	0.3691
beta 5	0.006	0.2856	0.0037
gamma 1	0.0173	0.0802	0.0030
gamma 4	0.0475	0.2843	0.0288
gamma 6	0.833	0.3645	0.6465
gamma 7	0.0032	0.5030	0.0034
gamma 8	0.0687	0.6370	0.0932
gamma 9	0.0159	0.7229	0.0245
K-x-rays	0.0467	0.0307	0.0030
Internal Conversion Auger Electrons L-x-rays		0.0228	

to 0.0030. All other gammas were considered insignificant for the purpose of these calculations (Table 1).

BIOLOGICAL DISTRIBUTION

Only the total-body retention data lends itself to the determination of actual biological half-lives. All other tissues were assumed to take up maximally the ^{131}I-19-iodocholesterol instantaneously with biological elimination, equal to the long biological half-life determined for whole-body retention.

Since no human data are currently available for liver or gonads, dog tissue concentrations were used.

Total-body retention. Data necessary for calculating the dose to the total body were obtained by collecting excreta from patients injected with a single i.v. dose of the compound. The total-body retention values given in Table 2 have been corrected for decay to time of dose; therefore the results represent biological elimination only.

Using a computer program, NONLIN (*12*), the best least-squares fit was obtained for the observed data when a bi-exponential function was used. The general form for this function is:

$$F(t) = F_1e^{-\lambda_1 t} + F_2e^{-\lambda_2 t}$$

The parameters obtained and their standard deviations were:

$$F_1 = 0.566 \pm 0.080 \quad \lambda_1 = 0.0026 \pm 0.0007\ hr^{-1}$$
$$F_2 = 0.611 \pm 0.064 \quad \lambda_2 = 0.025 \pm 0.007\ hr^{-1}$$

Therefore the fraction of the dose remaining as a function of time was summarized by the following normalized equation:

$$F(t) = 0.481e^{-0.0026} + 0.519e^{-0.026t} \quad (1)$$

Figure 1 gives the semi-log plot of the fraction of dose remaining as a function of time. The circles indicate the actual observed values given in Table 2. The squares represent the values calculated by the computer using Eq. 1. The observed and calculated percentage dose remaining as well as the percentage deviation (represented by Eq. 2) are given in Table 2.

$$\%\ \text{deviation} = (\text{obs.} - \text{calc.})\ (100)/\text{calc.} \quad (2)$$

TABLE 2. PERCENT* TOTAL-BODY RETENTION OF INTRAVENOUSLY ADMINISTERED ^{131}I-19-IODOCHOLESTEROL IN HUMANS

Patient No.	Time after injection (days)										
	1	2	3	4	5	6	7	8	9	10	11
1	87.5	55.0	40.0	33.5							
2	83.2	51.4	41.9	36.5	26.1	23.6	22.8	21.7	20.8	20.5	20.3
9	89.1	79.2	65.7	54.7							
18	91.9	82.3	66.4	62.5	59.5	57.8	54.2	53.5	52.1		
22	74.9	72.9	57.6	52.6							
27	78.2	61.6	53.2	45.9	42.9	42.6	41.5	40.0	39.4	37.9	36.9
31	99.9	81.7	65.8								
36	87.2	64.8	52.4	46.8	37.6	32.2	30.3	29.3	28.7	27.7	26.9
38	87.2	77.8	67.2	62.7	61.0						
Mean	86.7	69.6	56.7	49.4	45.4	39.1	37.2	36.1	35.2	28.7	28.0
± s.d.	±7.3	±11.8	±10.6	±10.8	±14.8	±14.7	±13.7	±13.8	±13.6	±8.7	±8.4
Calc. values	87.0	68.6	57.3	49.8	44.6	40.7	37.6	34.9	32.6	30.5	28.6
% Dev.†	−0.3	1.4	−1.0	−0.9	1.8	−4.1	−1.0	3.3	7.7	−6.3	−2.2

* Corrected for decay to time of dose administration.
† % deviation = (obs.-calc.) (100)/calc.

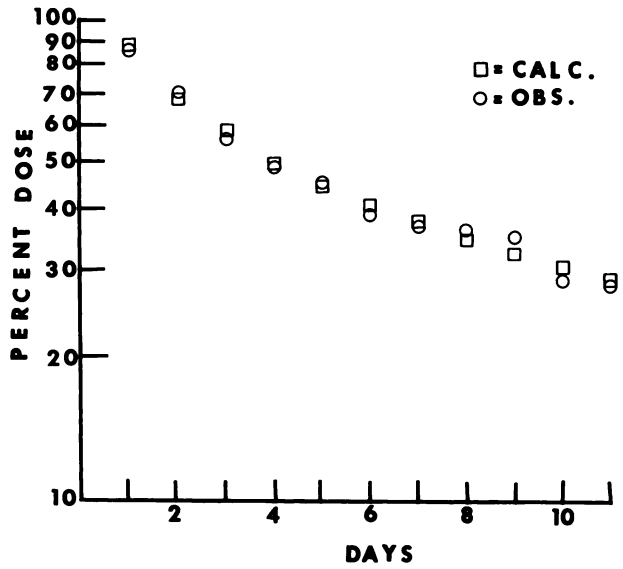

FIG. 1. Total-body retention of ^{131}I-19-iodocholesterol after single i.v. dose administration. Data from nine patients given in Table 2 is corrected for decay to time of dose.

Distribution of ^{131}I in tissues. Tables 3 and 4 give human tissue-distribution data. The ^{131}I-19-iodocholesterol distribution in liver, testes, and ovaries obtained from dogs is given in Table 5. The ^{131}I-19-iodocholesterol distribution data in dogs indicated an increased uptake in the liver and gonads. Therefore the data were used as a first-order approximation to the actual tissue concentrations in humans.

The fraction of dose in all tissues as a function of time was described by

$$F(t) = fe^{-(\lambda_p+\lambda_1)t} \qquad (3)$$

where λ_p is the physical decay constant and $\lambda_1 = 0.0026$.

ABSORBED-DOSE ESTIMATES

Absorbed-dose estimates were made using the MIRD pamphlets. These absorbed-dose estimates are the only means by which we can evaluate radia-

TABLE 3. PERCENT DOSE/GRAM* WHOLE HUMAN BLOOD

No. Patient	Time after injection† (days)								
	1	2	3	4	5	6	7	8	9
1	0.00439	0.00177	0.00137	0.00058	0.00038	—	0.00022	0.00018	0.00013
2	0.00279	0.00172	0.00119	0.00079	0.00043	—	—	—	—
9	0.00552	0.00387	0.00253	0.00099	0.00088	—	—	—	—
18	0.00480	0.00230	0.00136	0.00098	0.00064	—	—	—	—
101	0.0014	0.0008	0.0006	0.0003	—	—	—	—	—
102	0.00286	0.0012	0.00066	0.00037	—	—	—	—	—
Mean	0.00363	0.00194	0.00128	0.00067	0.00058	—	0.00022	0.00018	0.00013
± s.d.	±0.00154	±0.00108	±0.00070	±0.00030	±0.00023	—	—	—	—

* Corrected for decay to time of dose administration.
† Single i.v. dose administration.

TABLE 4. TISSUE DISTRIBUTION OF ^{131}I-19-IODOCHOLESTEROL IN HUMANS

Patient No.	Days	% dose/gm*						
		Adrenal	Tumor	Fat	Skin	Muscle	Lymph	Liver
1a	7	0.050	—	—	—	—	—	—
1b	5	0.044	—	—	—	—	—	—
1c	13	0.030	—	—	—	—	—	—
1d	4	0.020	—	—	—	—	—	—
1e	3	0.009	—	—	—	—	—	—
1	10	—	<MDA	<MDA	<MDA	<MDA	<MDA	0.001
9	10	0.130	0.197	0.010	—	0.001	—	—
10	3	0.013	—	0.003	0.005	0.003	—	0.016
15	5	0.123	<MDA	—	—	<MDA	—	—
21	28	0.026	0.023	<MDA	<MDA	0.001	—	—
27	19	0.219	0.390	0.004	0.003	0.002	—	—
29	13	0.019	0.015	<MDA	<MDA	<MDA	—	—
30	6	0.044	—	<MDA	<MDA	<MDA	<MDA	—
33	4	0.010	—	<MDA	<MDA	<MDA	—	—
40	13	0.024	0.029	—	—	—	—	—
Mean	—	0.054	0.131	0.006	0.004	0.002	—	—

* Single i.v. dose administration. Corrected for decay to time of dose administration.

TABLE 5. TISSUE DISTRIBUTION OF ^{125}I-19-IODOCHOLESTEROL IN DOGS

Days	% dose per gram*		
	Liver	Testes	Ovaries
1	0.009	—	0.015
2	0.018	0.007	0.075
3	0.011	0.008	0.005
4	0.005	0.005	0.009
6	0.005	0.005	0.041
8	0.003	0.007	—
14	<MDA	0.003	—
Mean	0.008	0.006	0.029
± s.d.	0.006	0.002	0.029

* Single i.v. dose administration. Corrected for decay to time of dose administration.

tion risks associated with the use of ^{131}I-19-iodocholesterol as an adrenal diagnostic agent.

The absorbed-fraction for both betas and other nonpenetrating radiations were considered to be equal to 1.0. Therefore

$$\Sigma\Delta_\beta\phi_\beta + \Sigma\Delta_{np}\phi_{np} = \Sigma\Delta_\beta + \Sigma\Delta_{np} = 0.4135.$$

All other fractions used are tabulated in Table 6 and were determined by linear interpolation between the values tabulated in the MIRD pamphlets (*13*).

The calculations are based on the schema found in MIRD (*14*) according to the basic equation:

$$\bar{D}_{v\leftarrow r} = \frac{\tilde{A}}{m_v}\sum_{i=1}\Delta_i\phi_{i(v\leftarrow r)} \qquad (4)$$

where $\tilde{A}_r$ is the cumulative activity (μCi-hr), m_v is the mass (gm) of the target, Δ is the equilibrium-dose constant (gm-rad/μCi-hr), and ϕ is the absorbed fraction.

Calculations were performed for total body, adrenals, liver, testes, and ovaries. The absorbed-dose estimates to the organs were calculated by Eq. 5 as described by Cloutier (*15*):

$$\bar{D}_{organ} = \frac{\tilde{A}_{org}}{M_{org}}(.4135) + \left[\frac{\tilde{A}_{org}}{M_{org}} - \frac{\tilde{A}_{TB}}{M_{TB}}\right]\Sigma\Delta\phi_{org\leftarrow org} + \left[\frac{\tilde{A}_{TB} - \tilde{A}_{org}}{M_{org}}\right]\Sigma\Delta\phi_{org\leftarrow TB}. \qquad (5)$$

Total body. The absorbed radiation dose to the total body can be represented by

$$\bar{D}_{TB} = \tilde{C}_{TB}\,[0.4135 + \Sigma\Delta\phi_{TB\leftarrow TB}]\ \text{rad} \qquad (6)$$

where

$$\tilde{C}_{TB} = \frac{\text{Dose }(\mu\text{Ci})}{M_{TB}}\left[\frac{F_1}{\lambda_p + \lambda_1} + \frac{F_2}{\lambda_p + \lambda_2}\right]$$

and $\lambda_p = 0.0036\ \text{hr}^{-1}$.

If the dose is 1,000 μCi, then

$$\bar{D}_{TB} = 0.94\ \text{rad/mCi}.$$

Adrenals. Using Eq. 5, the adrenal dose was calculated as follows:

$$\bar{D}_{Ad} = \frac{\tilde{A}_{Ad}}{M_{Ad}}(0.4135) + \left[\frac{\tilde{A}_{Ad}}{M_{Ad}} - \frac{\tilde{A}_{TB}}{M_{TB}}\right]\Sigma\Delta\phi_{Ad\leftarrow Ad} + \left[\frac{\tilde{A}_{TB} - \tilde{A}_{Ad}}{M_{Ad}}\right]\Sigma\Delta\phi_{Ad\leftarrow TB}$$

where

$$\tilde{A}_{Ad} = \frac{(\text{Dose})(f)(M_{Ad})}{\lambda_p},\ \tilde{A}_{TB} = \text{Dose}\left[\frac{F_1}{\lambda_1 + \lambda_p} + \frac{F_2}{\lambda_2 + \lambda_p}\right] \text{ and } M_{Ad} = 15.7.$$

Since tables were not available for $\phi_{Ad\leftarrow Ad}$, these values were estimated by assuming the adrenal glands to be small ellipsoids, each weighing approximately 8 gm. These values were determined from Table 8 in MIRD Pamphlet No. 8 and are given in Table 6 of this paper.

The calculated absorbed dose to the adrenal gland was 49.0 rad/mCi.

Liver. The absorbed dose to the liver was calculated using Eq. 5 and the tissue data in Table 5. The absorbed radiation to the liver was 7.1 rad/mCi.

Gonads. Table 5 and Eq. 5 were also used for the calculation of the absorbed radiation dose to the gonads. To determine $\phi_{gonad\leftarrow TB}$, the assumption was made that the activity is considered as a central point source in a 70-kg ellipse. Therefore (the M_{org} in the third expression of Eq. 5 becomes M_{TB} for the gonads. Using the above assumption, the determined dose estimate given is the maximum radiation absorbed dose rather than the average dose.

The calculated absorbed dose to the testes was 4.8 rad/mCi and 20.7 rad/mCi to the ovaries.

DISCUSSION

Optimum adrenal imaging using ^{131}I-19-iodocholesterol is accomplished 5–14 days after dose administration; thus a short physical half-life is precluded. The only radionuclides of iodine with the requisite physical half-lives are ^{125}I and ^{131}I. Because of the depth of the adrenal glands in human tissue and the weak gamma photon (0.035 MeV) of ^{125}I, this radioisotope is not satisfactory. This leaves ^{131}I as the only applicable radioisotope of iodine-suitable cholesterol labeling. Unfortunately, to obtain the necessary gamma component of ^{131}I, we must accept the associated beta contribution to the radiation dose.

Current studies are in progress to obtain actual

TABLE 6. ABSORBED FRACTIONS USED FOR ^{131}I-19-IODOCHOLESTEROL DOSIMETRY CALCULATIONS

			ϕ								
Radiation	$\bar{E}$	ni	tb<tb	ad<tb	ad<ad*	1<1	1<tb	t<t	t<tb†	o<o	o<tb†
Gamma 1	.0802	.0030	.440	.00010	.016	.2097	.0133	.0519	.583	.0221	.583
Gamma 4	.2843	.0288	.338	.00006	.017	.1580	.0108	.0437	.493	.0205	.493
Gamma 6	.3645	.6465	.338	.00009	.018	.1570	.0106	.0440	.488	.0214	.488
Gamma 7	.5030	.0034	.339	.00003	.018	.1569	.0101	.0446	.480	.0229	.480
Gamma 8	.6370	.0932	.335	.00013	.018	.1534	.0098	.0437	.472	.0221	.472
Gamma 9	.7229	.0245	.331	.00012	.018	.1512	.0096	.0431	.467	.0216	.467
K-x-rays	.0307	.0030	.766	.00021	.076	.5337	.0219	.2032	.955	.0960	.955
$\Sigma\Delta\phi$	—	—	.2723	.00008	.146	.1270	.0080	.0358	.391	.0174	.391

* Values obtained from Table 8, MIRD Pamphlet No. 8, *J Nucl Med* (Suppl. No. 5): 31, 1971.

† Values obtained from Table 4, MIRD Pamphlet No. 3, *J Nucl Med* (Suppl. No. 1): 34, 1968.

tissue concentrations of ^{131}I-19-iodocholesterol in human liver, testes, and ovaries. Initial results indicate that gonadal concentration in humans is about a factor of ten less than that observed in the dog. Because of the limited available human data for these tissues, we conservatively estimate the absorbed radiation dose in the human from the dog data available where sufficient scientific data exists.

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